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AUTHOR(S):

TOMOMASA, Hiroshi; SHIMIZU, Hirofumi; SATO, Satoshi; ADACHI, Yoichi; ASHIZAWA, Yoshio; KAMIYAMA, Yutaka; OKANO, Yoshinori; ... IIZUMI, Tatsuo; UMEDA, Takashi; YAZAKI, Tsunetada

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CLINICAL STUDY OF TESTICULAR GERM CELL TUMORS

Hiroshi TOMOMASA, Hirofumi SHIMIZU, Satoshi SATO, Yoichi ADACHI, Yoshio ASHIZAWA, Yutaka KAMIYAMA, Yoshinori OKANO, Mika SATO, Takashi YOSHII, Tatsuo IIZUMI and Takashi UMEDA

From the Department of Urology, Teikyo University School of Medicine

Tsunetada YAZAKI

From the Department of Urology, Meisei-kai Yamato Hospital

A clinical statistical analysis on 65 patients with 68 testicular germ cell tumors was performed. Thirty-six testes (53.7%) had seminomas and the remainder non-seminomatous germ cell testicular tumors (NSGCTTs). Of the seminomas, 31 (88.6%) were in stage I and the others showed distant metastases at presentation. Of the 32 NSGCTTs, 22 (68.8%) were in stage I. The average ages of the patients with seminomas and NSGCTTs were 40.4 and 29.9 years, respectively. Thirty-nine patients (60.0%) had tumors on the right side, 23 (35.4%) on the left and 3 (4.6%) in both testes. Five patients had a past history of cryptorchidism. Chief complaints in 49 patients (73.1%) were a painless scrotal mass. The interval from clinical onset to presentation was longer in seminoma patients than in NSGCTT patients (10.9 months on average versus 3.4 months). Immunosuppressive acidic protein (IAP) was a useful diagnostic tumor marker as well as α-feto protein (AFP), β-human chorionic gonadotropin (β-hCG) and lactic dehydrogenase (LDH). We adopted a surveillance policy in more than half of the stage I patients and obtained acceptable results. In the remaining cases, therapies including combination chemotherapy, radiation and salvage operation were performed after orchiectomy. The three-year survival rate was 98.0, 100.0 and 26.7%, for stage I, II and III patients respectively.

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Key words: Testicular germ cell tumor, Clinical statistics, Tumor markers, Treatment result

INTRODUCTION

Recent improvement in diagnostic and therapeutic methods has resulted in an excellent clinical outcome in patients with testicular germ cell tumors[1], but there is still debate on the therapy for stage I disease, insufficient prognosis in advanced disease with distant metastasis and the fertility of patients of reproductive age[2]. In this report we summarize the clinical features of patients with testicular germ cell tumors treated at the Department of Urology, Teikyo University School of Medicine in the 14 years from May 1986 to April 2000.

PATIENTS AND METHOD

The 65 patients with 68 testicular germ cell tumors treated at our institution in the 14 years from May 1986 to April 2000 were recruited for this study. Extragonadal germ cell tumors and other testicular tumors such as benign tumors, metastatic tumors and hematogenic tumors were excluded. Statistical significance was calculated by Student's *t*-test, chi-square test and the Kaplan-Meier test. SPSS for Macintosh release 4.0 was used for the analyses and the results were considered significant when a p value was lower than 0.05.

RESULTS

1. Pathological classification and clinical stages

The pathological types and clinical stages of tumors were classified according to the pathological classification of the Japanese Urological Association[3] (Table 1, 2). In 67 testes, 40 (59.7, 95% confidence interval 47.9 to 71.5) had one histological type including 36 seminomas (53.7%, 41.7 to 65.8). The other 27 testes (40.3%, 28.5 to 52.1) had two or more

Table 1. Pathological types of germ cell tumors

Pathological types	Number of cases (%)
Tumors of one histological type	
Seminoma	36 (53.7)
Mature teratoma	1 (1.5)
Embryonal carcinoma	2 (3.0)
Yolk sac tumor	1 (1.5)
Tumors of more than one histological type	
Seminoma+1 component	2 (3.0)
Seminoma+2 components	7 (10.5)
2 componnents	7 (10.5)
3 components	6 (9.0)
4 or more components	5 (7.5)
Total	67 (100.0)

Table 2. Clinical stages in patients with testicular germ cell tumors. NSGCTT, non-seminomatous germ cell testicular tumor

Stages	Seminoma (%)	NSGCTT (%)	Total (%)
I	31 (88.6)	22 (68.8)	53 (79.1)
IIA	1 (2.9)	5 (15.6)	6 (9.0)
IIB	2 (5.7)	0 (0.0)	2 (3.0)
IIIA	0 (0.0)	1 (3.1)	1 (1.5)
IIIB	0 (0.0)	3 (9.4)	3 (4.5)
IIIC	1 (2.9)	1 (3.1)	2 (3.0)
Total	35 (100.0)	32 (100.0)	67 (100.0)

histological types. Clinical stages were described discretely for seminomas and non-seminomatous germ cell testicular tumors (NSGCTTs). Thirty-one cases of seminomas (88.6%, 77.9 to 99.3) were classified as stage I, 3 (8.6%, 0.0 to 18.0) as stage II and 1 (2.9%, 0.0 to 8.5) as stage III. Of NSGCTT cases, 22 (68.8%, 52.4 to 85.1) were diagnosed as stage I, 5 (15.6%, 2.8 to 28.4) as stage II and 5 (15.6%, 2.8 to 28.4) as stage III.

2. Age distribution and laterality

The patient's ages at presentation are shown in Fig. 1. Metachronous bilateral cases were recorded as two cases. The most frequent age range for seminomas was 40 to 49 years with an average of 40.8±12.7 (average±standard deviation). In patients with NSGCTT, ages between 20 and 29 were the most frequent with an average of 29.2±8.5 years. There was a significant difference in the average age ($p=0.000$, t-test). As shown in Table 3, 39 (60.0%, 48.0 to 72.0) patients had the disease on the right side: It was significantly more frequent on the right than on the left ($p=0.042$).

Table 3. Laterality of the tumors. Lesions were significantly more numerous on the right than on the left ($p=0.042$, chi-square)

	Seminoma (%)	NSGCTT (%)	Total (%)
Right	20 (58.8)	19 (61.3)	39 (60.0)
Left	12 (35.3)	11 (35.5)	23 (35.4)
Bilateral	2 (5.9)	1 (3.2)	3 (4.6)
Total	34 (100.0)	31 (100.0)	65 (100.0)

3. Clinical onset and past histories

Three of the patients with a seminoma (8.8%, 0.0 to 18.5) had a past history of ipsilateral cryptorchidism. One of them had not been treated and the others had received orchidopexy. In NSGCTT patintts, 2 (6.7%, 0.0 to 15.7) had a past history of orchidopexy for cryptorchidism. One of them had it on the contralateral side. One seminoma patient had been treated for retroperitoneal extragonadal germ cell tumor 9 years before the onset of the scrotal disease. Two patients had a past history of testicular injury. The chief complaints of the patients are listed in Table 4. Forty-nine patients (73.1%, 62.4 to 83.8)

Table 4. Chief complaints in patients with testicular germ cell tumors. NSGCTT, non-seminomatous germ cell testicular tumor

Chief complaint	Seminoma (%)	NSGCTT (%)	Total (%)
Painless scrotal mass	30 (85.7)	19 (59.4)	49 (73.1)
Painful scrotal mass	4 (11.4)	9 (28.1)	13 (19.4)
Back pain	1 (2.9)	1 (3.1)	2 (3.0)
Others	0 (0.0)	2 (6.3)	2 (3.0)
Total	35 (100.0)	32 (100.0)	67 (100.0)

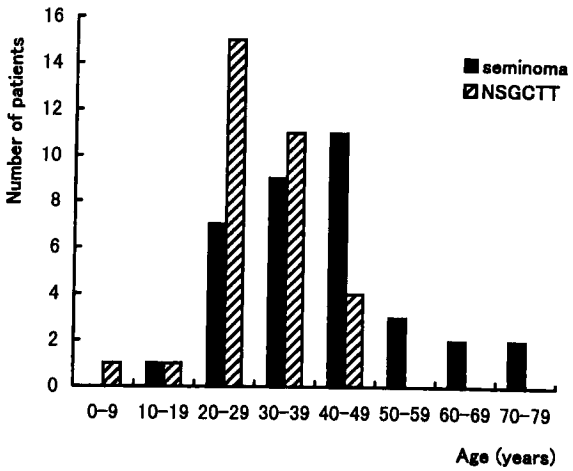

Fig. 1. Age distributions of patients with testicular germ cell tumors. Average ages of patients with seminoma and NSGCTT were 40.8 and 29.2 years old ($p=0.000$, t-test). NSGCTT, non-seminomatous germ cell testicular tumor.

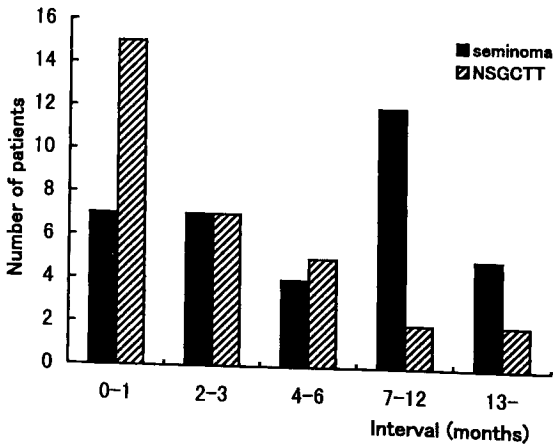

Fig. 2. Interval between clinical onset and presentation. Average length of the period was longer in seminoma patients than in NSGCTT. NSGCTT, non-seminomatous germ cell testicular tumor.

presented with the chief complaint of scrotal swelling without pain, whereas 13 patients (19.4%, 9.9 to 28.9) had a painful mass. The patients with NSGCTT tended to have pain but the difference was not significant (p=0.103, chi-square). Back pain due to a metastatic disease was the reason for hospitalization in two patients. The intervals from the clinical onset to hospitalization are summarized in Fig. 2. For patients with seminomas the average period was 10.9 ±20.1 months, but 3.4±4.7 months for NSGCTT patients. The difference was statistically significant (p=0.023, *t*-test) suggesting more rapid growth of NSGCTTs. The average maximum diameter of the specimen was 7.1±3.2 cm for seminomas and 8.3±3.9 cm for NSGCTTs (p=0.115, *t*-test).

Table 5. Positive rates of tumor markers. AFP and β-hCG were positive more frequently in NSGCTTs (p=0.000, p=0.027, chi-square)

	Seminoma (%)	NSGCTT (%)	Total (%)
AFP	2/30 (6.7)	21/29 (72.4)	23/59 (39.0)
β-hCG	8/30 (26.7)	14/25 (56.0)	22/55 (40.0)
LDH	21/34 (61.8)	13/24 (54.2)	34/58 (58.6)
IAP	13/30 (43.3)	6/20 (30.0)	19/50 (38.0)

LDH and IAP were positive more frequently in seminomas. The differences were not significant (p=0.563, p=0.341). NSGCTT, non-seminomatous germ cell testicular tumor; AFP, α-feto protein; β-hCG, β-human chorionic gonadotropin; LDH, lactic dehydrogenase; IAP, immunosuppressive acidic protein.

4. Tumor markers

Serum α-feto protein (AFP), β-human chorionic gonadotropin (β-hCG), lactic dehydrogenase (LDH) and immunosuppressive acidic protein (IAP) were examined as the tumor markers. The positive rates for these markers in seminomas and NSGCTTs are shown in Table 5. The positive rates for AFP and β-hCG were quite high in NSGCTT patiints (p=0.000, p=0.027), whereas IAP and LDH tended to be positive more frequently in seminoma patients (p=0.341, p=0.563).

5. Therapeutic strategy and clinical outcome

In cases without metastatic diseases, basically we recommended surveillance for both seminomas and NSGCTTs except for cases before 1988, when prophylactic radiation was used for stage I seminoma patients. Nevertheless, when microscopic invasion into vessels was found in the histopathological

Table 6. Initial treatments and outcome. NSGCTT, non-seminomatous germ cell testicular tumor.

Initial treatment	Number of patients (%)	Relapse (%)
Stage I		
Seminoma		
Surveillance	20 (64.5)	1 (5.0)
Adjuvant chemotherapy	7 (22.6)	
Adjuvant radiotherapy	4 (12.9)	
Total	31 (100.0)	
NSGCTT		
Surveillance	10 (45.5)	1 (10.0)
Adjuvant chemotherapy	12 (54.5)	1 (8.3)
Total	22 (100.0)	
Stage II		
Seminoma		
Radiotherapy	1 (33.3)	
Chemotherapy, radiotherapy	1 (33.3)	
Chemotherapy, Salvage operation	1 (33.3)	
Total	3 (100.0)	
NSCGTT		
Chemotherapy	3 (60.0)	
Chemotherapy, Salvage operation	2 (40.0)	
Total	5 (100.0)	
Stage III		
Seminoma		
Chemotherapy, radiotherapy	1 (100.0)	
Total	1 (100.0)	
NSGCTT		
Chemotherapy, radiotherapy	1 (10.0)	1 (100.0)
Chemotherapy, Salvage operation	4 (80.0)	2 (50.0)
Total	5 (100.0)	

specimens or the tumor included an embryonal carcinoma component, we recommended prophylactic chemotherapy or radiation on adequate informed consent according to the concept that these factors have a significant correlation with the probability of metastasis[4,5]. In patients with metastatic lesions, combination therapies including cisplatin based chemotherapy, radiation and surgery were indicated. Primary therapies in each stage are summarized in Table 6. For 20 (64.5%) patients with stage I seminomas, surveillance was selected, whereas prophylactic radiation or chemotherapy was performed in 4 (12.9%) and 7 cases (22.6%) respectively. One of them without any adjuvant therapies had recurrent disease in the retroperitoneum, received chemotherapy and radiation, and thereafter has been followed up without any sign of metastasis. Of 10 (45.5%) cases with NSGCTT that had been followed up according to a surveillance policy, one patient had subsequent metastatic disease in the thoracic lymph node and died of the disease in spite of treatment with combination chemotherapy. The other 12 (54.5%) patients received prophylactic chemotherapy. In one of them, salvage surgery was performed for a retroperitoneal metastatic lesion.

In patients with metastatic disease, cisplatin-based-chemotherapy was performed except for one with stage IIA seminoma, who received radiation therapy. Surgical removal of the metastatic lesions was performed in 7 patients before (2 cases) or after (5 cases) the chemotherapy. The metastatic diseases were in retroperitoneal lymph nodes in 4, lungs in 2 and brain in 1 case. Radiation therapy was combined with chemotherapy in 3 cases.

Actuarial survival analyses by the Kaplan-Meier method were performed according to the stages and pathological classification (Fig. 3a, b). No patients died in stage II, but 2 (3.9%) and 3 (50%) patients died in stages I and III, respectively, the three-year survival rate for patients in stages I, II and III was 98.0% (95% confidence interval 94.0 to 100.0), 100.0% and 26.7% (0.0 to 70.9), respectively. There was a statistically significant difference between stages I and III and between stages II and III (p=

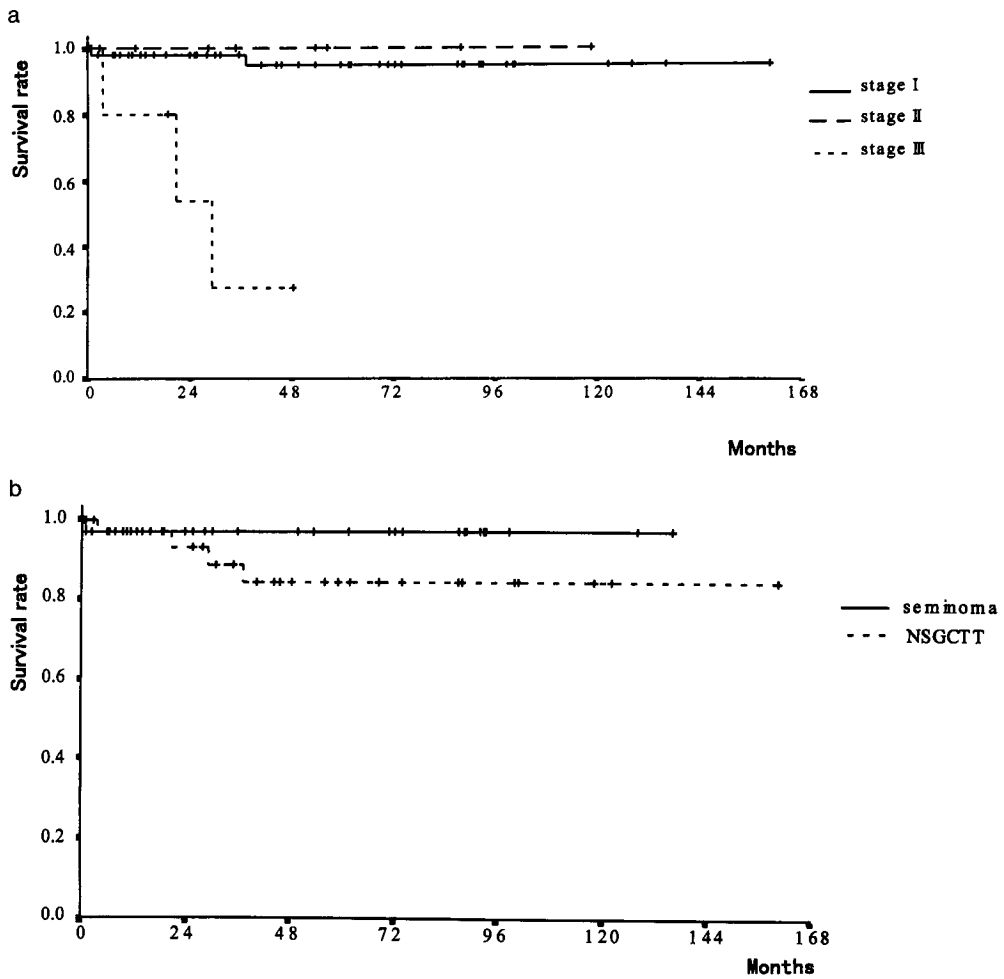

Fig. 3. Survival rate of the patients with testicular cancers according to the stage (Fig. 3a) and pathological type (Fig. 3b). There are statistically significant differences between stages I and III and stages II and III (p=0.000 and p=0.016). The differences between stages I and II and in pathological type are not significant (p=0.586 and p=0.222).

0.0001 and p=0.016, p=0.5861 between stage I and II). The three-year survival rate was 96.9% (90.8 to 100.0) and 88.6% (76.3 to 100.0), for seminomas and NSGCTTs, respectively; the difference was not statistically significant (p=0.222).

DISCUSSION

Prevalence of testicular cancers is reported to be 0.7 to 1.1 in 100,000 males[6]. In previous reports, the most frequent age group was twenties to thirties and the average age was higher in seminoma patients than in NSGCTT patients[7,8] This is compatible with our findings, in which the average age of seminoma patients was significantly higher than that of NSGCTT patients. This is also supported by the reported description[9], that the peak incidence of seminomas is at 35 to 39 years, whereas embryonal carcinoma and teratocarcinoma occur between the ages of 25 and 35 years, yolk sac tumors in infancy and childhood, pure teratomas in children and malignant lymphomas over the age of 50 years. In our series, a right-sided disease was significantly more numerous than the left. Some of the reports were consistent with our data[6,9], whereas others denied the preponderance of the right side[8]. Past history of orchidopexy for cryptorchidism is a well-known risk factor of testicular cancers. Approximately 10% of patients with testicular cancers are reported to have a past history of cryptorchidism, and the prevalence is apparently higher than in normal males[10]. In our series, five patients out of 65 (7.7%) had a past history of cryptorchidism, one of whom had not yet been treated while the others had received orchiopexy. Although one of them had subsequent malignancy on the contralateral side, the frequency of a past history was consistent with previous reports. AFP and β-hCG are well known tumor markers for testicular cancers, in which the positive rates are higher in NSGCTTs[8,11]. Although not so specific as these markers, LDH was also useful in those cases in which no other markers were high. Especially in seminoma patients it may be the only marker that reflects the spread of the disease. In our series, IAP values were high in 19 cases out of 50 (38.0%) and the positive rate was also substantial in seminoma patients (13/30, 43.3%). IAP is not specific but in some urological malignancies is useful for diagnosis, estimating the extent of the disease, prediction of the outcome and early detction of the recurrence[12]. Especially in patients with renal cell carcinomas, IAP was correlated with the tumor stage and was a significantly independent variable for survival[12,13]. Concerning testicular cancers, Miki et al.[14] demonstrated the significance of IAP in diagnosis and staging. In their series, positive rates in stages II and III were significantly higher than in stage I. Unfortunately, our series was not so large as to allow comparison of stages. Further accumulation of cases is expected.

Recent improvement in diagnostic methods such as computed tomography and tumor markers has facilitated early detection of recurrence after orchiectomy. Furthermore, progression in combination chemotherapy provides good results in the treatment of metastatic lesions. With this background, for stage I seminoma patients as well as NSGCTT patients, the surveillance policy has come to be widely accepted[4,15] In our series, out of 20 seminoma patients who had been followed up according to the surveillance policy, only 1 patients (5%) had recurrence and none died. Of 10 NSGCTT patients, 2 (20%) had recurrence and one died (10%). This patient refused prophylactic chemotherapy although an embryonal carcinoma component was included. Taking this into consideration, our surveillance results were acceptable. In this series we recognized the existence of embryonal carcinoma, regardless of its volume as a risk factor. Recently, however, several reports have demonstrated that the percentage of the embryonal carcinoma component had a strong impact on probability of recurrence[16] Sogani et al. reported the clinical outcome of surveillance for clinical stage I germ cell tumors except for pure seminomas, pure choriocarcinomas and stage T2-T4 tumors. The relapse rate in their cases of predominant embryonal carcinoma histology was as high as 46%. Considering the hazardous effects of chemotherapy such as secondary cancers, neurotoxicity, impaired renal function and infertility, the need for prophylactic chemotherapy should be discussed in each case, according to the patient's age, marital status and complications. As for advanced cases, none of the patients in our series with stage II disease died. Of those in stage III, however, 3 out of 6 patients (50%) died of the disease and the three-year survival rate was no more than 26.7%. Early in this series, we selected a combination of cisplatin, vinblastine and bleomycin (PVB)[18] as the initial treatment regimen. Recently, however, vinblastine was replaced with etoposide on the assumption that the most effective regimen should be used as the initial treatment regimen (PEB)[19]. When applied to the cases with respiratory disease or for prophylactic purposes, bleomycin was excluded (PE)[20]. In cases with disease refractory to the initial treatment, ifosfamide was added (PIE)[21] Radiation therapy was combined if the lesions were localized. Surgical removal of the residual masses was performed to confirm whether the previous regimens had eradicated the tumor cells. In spite of these combination therapies, our results in stage III patients were not satisfactory. Recent reports advocated the effictiveness of high dose chemotherapy

with autologous bone marrow transplantation (ABMT) or peripheral blood stem cell transplantation (PBSCT) for advanced testicular cancers[22,23], but these powerful regimens may also induce lethal side effects. As of now, we should continue further clinical trials, looking forward to improvements in treatment regimens and in the prevention of side effects.

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和文抄録

精巣胚細胞腫瘍の臨床的検討

帝京大学医学部泌尿器科学教室（主任：梅田　隆教授）
友政　宏，清水　弘文，佐藤　聡，足立　陽一
芦沢　好夫，上山　裕，岡野　由典，佐藤　ミカ
吉井　隆，飯泉　達夫，梅田　隆

明星会大和病院泌尿器科（院長：矢崎恒忠）
矢崎　恒忠

精巣胚細胞腫瘍65例68精巣を臨床的に検討した．36精巣（53.7%）はセミノーマで，残りは non-seminomatous germ cell testicular tumor (NSGCTT) であった．セミノーマ症例のうち31例（88.6%）はⅠ期でそれ以外は受診時に転移巣を有していた．NSGCTT のうち22例（68.8%）はⅠ期であった．セミノーマおよび NSGCTT 症例の平均年齢はそれぞれ40.4，29.2歳であった．39例（60.0%）は右側，23例（35.4%）は左側，3例（4.6%）は両側性であった．5例は停留精巣の既往を有していた．49例（73.1%）において主訴は無痛性精巣腫大であった．症状発現から受診までの期間は NSGCTT 症例よりセミノーマの方が長かった（平均10.9カ月と3.4カ月）．Immunosuppressive acidic protein (IAP) は alpha-feto protein (AFP)，beta-human chorionic gonadotropin (beta-hCG)，lactic dehydrogenase (LDH) と共に腫瘍マーカーとして有用であった．Ⅰ期症例の過半数においては surveillance policy に順じて経過観察とした．その他の症例には補助療法として多剤併用抗癌化学療法，放射線療法，手術療法を追加した．3年生存率はⅠ期で98.0%，Ⅱ期で100.0%，Ⅲ期で26.7%であった．

（泌尿紀要 **47**：389-395，2001）